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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,327	09/02/2004	Shingo Hiramatsu	0210-0190PUS1	1247
2292 7590 10/31/2007 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747			EXAMINER SAJJADI, FEREDOUN GHOTB	
			ART UNIT 1633	PAPER NUMBER
			NOTIFICATION DATE 10/31/2007	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

## Office Action Summary

Application No.

10/506,327

Applicant(s)

HIRAMATSU ET AL.

Examiner

Fereydoun G. Sajjadi

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 17 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-24, 26-28 and 30-45 is/are pending in the application.
- 4a) Of the above claim(s) 1-20, 40 and 41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21-24, 26-28, 30-39 and 42-45 is/are rejected.
- 7) ☒ Claim(s) 31 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 8/17/2007.
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application
- ☐ Other: \_\_\_\_\_

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### **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### ***Request for Continued Examination***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 17, 2007 that includes a response to the final office action dated April 18, 2007, has been entered. Claims 1-24, 26-28 and 30-45 are pending in the application. Claims 1-24, 26, 28, 30-32, 34 and 36-38 have been amended, claims 25 and 29 were cancelled, and claims 42-45 were newly added. Claims 1-20, 40, and 41 remain withdrawn from further consideration, with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 21-24, 26-28, 30-39 and 42-45 are under current examination.

#### ***Response to Information Disclosure Statement***

Documents CA-CD, CB and BB have been considered by the examiner and indicated as such on form on Supplemental Form SB/08.

#### ***Response & New Claim Objections***

Claims 21-24 stand objected to for containing spelling and grammatical errors; and claims 31 and 33-38 stand objected to under 37 CFR 1.75(c) as being in improper multiple dependent claims, in the office action dated April 18, 2007. Applicants' amendment of claims 21-23 to substitute "active" with "expressed", deleting "piggyBack" in claim 21, and correcting improper multiple dependency language of claims 31 and 38, obviates the grounds for rejection of claims 21-24, 31 and 33-38. Thus, the objection to claims 21-24, 31 and 33-38 is hereby withdrawn.

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Claim 31 is newly objected to, because 37 CFR § 1.121 (c) states: Amendments to a claim must be made by rewriting the entire claim with all changes (e.g., additions and deletions) as indicated in this subsection, except when the claim is being canceled. Claim 31 has been amended to read “transposons present on both sides of the gene cassette any one of claims 21 to 23”. The wording “according to” has been omitted from the claim. Appropriate correction is required.

Applicant should note that the submission of any further defective amendments will result in a notice of non-compliant amendment.

***Response to Claim Rejections - 35 USC § 112***

Claims 21, 25, 26 and 28 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite, in the previous office action dated April 18, 2007. The cancellation of claim 25 renders its rejection moot. Applicants' amendment of claim 28, to provide consistency with the language of base claims 22 and 23, and the amendment of claim 21, adopting language previously suggested by the examiner, obviate the grounds for rejection of the claims. Thus, the rejection of claims 21, 26 and 28 is hereby withdrawn.

***Response to Claim Rejections - 35 U.S.C. § 102 & 103***

Claims 22, 23, 25, 27, 29 and 30 were rejected under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (Acta Biochimica et Biophysica Sinica 33(1): 112-116, Jan. 2001) as evidenced by Zhang et al. (Acta Biochimica et Biophysica Sinica 31(2): 119-123, 1999) and GenBank Acc. No. AF226688. Claims 26 and 28 were rejected under 35 U.S.C. 102(b) as anticipated by or in the alternative, under 35 U.S.C. 103(a) as obvious over Zhao et al. (Acta Biochimica et Biophysica Sinica 33(1): 112-116, Jan. 2001) as evidenced by Zhang et al. (Acta Biochimica et Biophysica Sinica 31(2): 119-123, 1999) and GenBank Acc. No. AF226688, and further in view of Zhou et al., Nucleic Acids Res. 28(12): 2413-2419, in the previous office action dated April 18, 2007. Applicants' cancellation of claims 25 and 29 renders their rejection moot. In view of Applicants' claim amendments of base claims 21-23 to introduce the limitation

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for an inverted repetitive sequence of a piggyBac transposon in the gene cassette, said limitation not present in the cited references, and thus obviating the ground of rejection, the previous rejection is hereby withdrawn.

Applicants' should note that the previous rejection set forth on pp. 5-6 of the previous office action dated April 18, 2007 included claims 29 and 30 (see first line of the rejection on p. 5). Therefore Applicants are incorrect in their statement that claim 29 was previously non-anticipated.

### ***Response & New Claim Rejections - 35 U.S.C. § 103***

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 21-23, 25, 27, 29, 30, 32, and 38 stand rejected and claims 24, 26, 28, 31-39, and 42-45 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al., US 2002/0137211 in view of Zhao et al. (Acta Biochimica et Biophysica Sinica 33(1): 112-116, Jan. 2001); Zhang et al. (Acta Biochimica et Biophysica Sinica 31(2): 119-123, 1999) and GenBank Acc. No. AF226688. Applicants' cancellation of claims 25 and 29 renders their rejection moot. The rejection set forth on pp. 7-9 of the previous office action dated April 18, 2007 is maintained for claims 21-23, 25, 27, 29, 30, 32, and 38 and is further applied to claims 24, 26, 28, 31-39, and 42-45, for the reasons of record.

Applicants traverse the rejection, separately setting forth distinguishing features between the presently claimed invention and the disclosures of Zhao et al. and Zhang et al.; Zhou et al.; and again separately, Liu et al. Applicants' arguments have been fully considered, but are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). However, for completeness of the record, the key points of Applicants' arguments are addressed as follows:

With regard to Applicants' assertion that the gene of Zhao et al. and Zhang et al. does not comprise piggyBac transposon inverted terminal repeats, and that the homologous recombinant transgenic silkworm produced by the gene targeting of the fibroin H chain would result in the



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inability to form silk, it should be noted that such deficiency is cured by the disclosure of Liu et al., describing the introduction of a heterologous gene flanked by transposon inverted repeats in *Bombyx mori* to produce 30% of the total silk proteins (Abstract).

As previously indicated on the record, Zhao discloses a transgenic silkworm with a genome comprising a "gene cassette" embraced by the instant claims. The gene cassette comprises, in order, the 5' end of the endogenous fibroin H-chain gene, including the promoter, exon I, intron I, and the 5' end of exon II terminated by a PstI site, fused in-frame to a GFP coding sequence, fused in frame to coding sequence for a synthetic fibroin like sequence, fused in frame to a 3' terminal portion of the endogenous fibroin H-chain gene, comprising the three Cys residues, and the endogenous genomic sequence flanking the 3' end of the Fib-H coding sequence, that was introduced into the gene targeting vector of Zhang et al. Liu et al. teach an alternative method, providing a design choice to a person of ordinary skill in the art for introducing a transgene into *Bombyx mori*, to express a heterologous protein. Said design choice amounting to combining prior art elements according to known methods to yield predictable results.

Regarding Applicants' arguments directed to the solubility of the transgene product and that it is impossible to produce and recover physiologically active protein from a transgenic silkworm produced using the genes disclosed by Zhao et al. and Zhang et al., it should be noted that the GFP and fibroin-like gene fusion was utilized by Zhang et al. as an exemplification. The authors state that gene targeting can be conducted on their transgenic silkworm to eliminate the fusion gene between gfp and synthetic fibroin-like gene and exchange it with another gene, for further improving the silk property or for obtaining desirable intermediates of another new transgenic silkworm, (last paragraph, p. 9). Therefore, a person of ordinary skill in the art would know that transgene expression in *Bombyx mori* is not limited to a GFP-Fibroin-like fusion gene, and that the aqueous solubility of a resulting heterologous protein would be an inherent property of the particular transgene introduced by the vector of Zhao et al. or Liu et al., and expressed in silk gland cells.

With regard to Applicants' arguments that the method disclosed by Zhao et al. and Zhang et al. differs in that only an exogenous protein is expressed, and that exogenous protein is not a fused protein with silkworm fibroin H chain protein; that the presently claimed invention

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provides a gene cassette capable of being expressed as a fused protein with silkworm fibroin H chain protein; that in the presently claimed invention the fibroin H chain gene is partially translated using a promoter expressed in silkworm silk gland and exogenous protein is expressed in the form of a fused protein; such is not found persuasive, because Zhao et al. disclose a transgenic silkworm with a genome comprising a gene cassette comprising, in order, the 5' end of the endogenous fibroin H-chain gene, including the promoter, exon 1, intron I, and the 5' end of exon II terminated by a PstI site, fused in-frame to a GFP coding sequence, fused in frame to coding sequence for a synthetic fibroin like sequence, fused in frame to a 3' terminal portion of the endogenous fibroin H-chain gene, comprising the three Cys residues, and the endogenous genomic sequence flanking the 3' end of the Fib-H coding sequence that include the transcription terminator. The GFP and fibroin-like coding sequences were inserted into the endogenous gene by gene targeting using the pUC53 vector of Zhang, such that the coding sequence for the repetitive regions of the Fib-H protein were replaced by the exogenous protein structural genes. See entire document, especially Section 2.2 and Fig. 1 (page 5), Fig. 2, and Fig. 5. Zhao et al. additionally state that in this manner the fusion gene could be placed under the regulation of the promoter of fibroin heavy chain, which can also be utilized for secretion of the N terminal signal peptide of the fibroin heavy chain gene, and that the 3' terminal sequence of the heavy chain gene was not altered, and the polyA sequence should not be affected and the 3 Cys residues at C-terminal of the gene product were not influenced. (page 5, section 2.2). Thus, contrary to Applicants' assertion, a fusion with the fibroin heavy chain gene is specifically taught by Zhao et al. resulting in GFP expression in the silk and cocoons produced by the transgenic silkworm (see Fig. 3, p. 6).

Applicants' arguments directed to the disclosure Zhou et al. are moot in view of the fact that Zhou et al. was not included as a prior art reference in the instant obviousness rejection.

With respect to Applicants' arguments directed to the disclosure of Liu et al., specifically, that in contrast to the gene described by Liu et al., disclosing the coupling of silkworm fibroin L chain and the spider dragline silk protein gene using a silkworm fibroin L chain promoter as a promoter expressed in silkworm silk glands, and a fibroin L chain terminator, the gene of the presently claimed invention differs in that it couples silkworm fibroin H chain and an exogenous protein gene, using silkworm fibroin H chain promoter and a fibroin H chain terminator,

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Applicants should note that such deficiency is cured by the teachings of Zhao et al., as outlined above, wherein the silkworm fibroin H chain was sequence was fused to a heterologous gene, using silkworm fibroin H chain promoter and a fibroin H chain terminator.

Liu et al. disclose a vector comprising a gene cassette encoding a fusion protein comprising spider dragline silk repetitive sequence inserted into the repetitive sequence of *B. mori* fibroin L-chain for making transgenic silkworms that then produce silk comprising the fusion protein as the L-chain. This vector and a second vector expressing piggyBac transposase are introduced into silkworm eggs to produce the transgenic silkworm. The gene cassette comprises in order: an inverted terminal repeat (ITR) of a piggyBac transposon; the promoter of the *B. mori* fibroin L-chain gene; the 5' part of a fibroin L-chain cDNA including 5' untranslated sequence and coding sequence of fibroin L-chain including the signal sequence; a foreign sequence encoding the repetitive amino acid region of spider dragline silk without a stop codon; the 3' part of the fibroin L-chain cDNA including the remainder of the L-chain coding sequence and 3' untranslated region; the transcription terminator sequence (polyA addition region) of the L-chain gene; and an ITR of a piggyBac transposon. The spider silk coding sequence is inserted into the coding sequence for the repetitive region of the L-chain. See entire document, especially Fig. 2, and ¶¶ 005-009, 0011-0012, 0014, 0039 and 0041. Therefore a person of ordinary skill in the art is provided a design choice by the teachings of Zhao et al. and Liu et al. to utilize either the fibroin H chain or L chain sequences in the construction of a transgene expression vector, to make the analogous construct using the fibroin H-chain gene sequences in place of the L-chain gene sequences. Said design choice amounting to combining prior art elements according to known methods to yield predictable results, as silk fibroin is made up of both heavy and light chains, and one of skill in the art would recognize that the H-chain gene sequences and L-chain gene sequences were equivalents for producing transgenic silk.

Applicants' arguments regarding the aqueous solubility of transgene products produced have been addressed above. Applicants' arguments stating that the simultaneous production of fibroin H and L chains in Liu et al. would be problematic are non sequitur, as such is also produced by the method of the instant invention. Further, the teachings of Zhao et al. cannot be ignored in a rejection based on the combination of references and their combined teachings as a whole.



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Thus, the rejection of claims 21-23, 25, 27, 29, 30, 32, and 38 is maintained, and further applied to claims 24, 26, 28, 31-39, and 42-45 for reasons of record, and the foregoing commentary.

### *Conclusion*

#### **No claims are allowable.**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

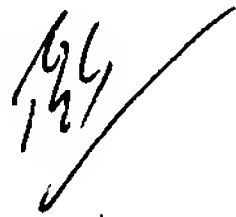
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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